PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70 PCT)

Applicant's or agent's file reference	**FOR FURTHER ACTION**	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416).
24991 WO		

International application No.	International filing date *(day/month/year)*	Priority Date *(day/month/year)*
PCT/EP 03/02969	**21/03/2003**	**22/03/2002**

International Patent Classification (IPC) or national classification and IPC
A61K48/00

Applicant
ORTHOGEN AG et al.

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 5 sheets, including this cover sheet.

   ☒ This report is also accompanied by ANNEXES, i.e., sheets of the description, claims and/or drawings, which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of **8** sheets.

3. This report contains indications relating to the following items:

I	☒	Basis of the report
II	☐	Priority
III	☐	Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
IV	☐	Lack of unity of invention
V	☒	Reasoned statement under 66.2 a)ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
VI	☐	Certain documents cited
VII	☐	Certain defects in the international application
VIII	☐	Certain observations on the international application

Date of submission of the demand
18/07/2003

Date of completion of this report
23/03/2004

Name and mailing address of the International Examination Authority:
Europäisches Patentamt
D-80298 München
Tel.: +49 89 2399-0 Tx: 523656 epmu d
Fax.: +49 89 2399-4465

Authorized officer

Ludwig, G.

Tel. +49 89 2399 8698

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International Application No. **PCT/EP 03/02969**

I. Basis of the report

1. With regard to the **elements** of the international application (*replacements sheets filed with the receiving Office on request according to Art. 14 are considered "originally filed" within the scope of this report and are not attached to it, since they do not include any changes (Rules 70.16 and 70.17)):*

Specification, pages:

1-40 **in the originally filed version**

Claims, No.:

1-39 **filed on March 2, 2004 with document of March 1, 2004**

Drawings, Sheets

1/11 – 11/11 **in the originally filed version**

2. With regard to the **language**: All the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language which is:

~ the language of a translation furnished for the purposes of international search (under Rule 23.1(b)).
~ the language of publication of the international application (under Rule 48.3(b)).
~ the language of the translation furnished for the purposes of international preliminary examination (under Rules 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the written opinion was drawn on the basis of the sequence listing:

~ Contained in the international application in printed form.
~ Filed together with the international application in computer readable form.
~ Furnished subsequently to this Authority in written form.
~ Furnished subsequently to this authority in computer readable form.
~ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
~ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

~ the description, pages:
~ the claims, No.:
~ the drawings, sheet:

5. ~ This opinion has been established as if (some of) the amendments had not been made, since they have been considered by the authority to go beyond the disclosure as filed, as indicated (Rule 70.2(c)).

(Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report)

6. Any other comments:

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Determination

Novelty (N)	Yes:	Claims	**2-4, 6-18, 21-29, 31-39**
	No:	Claims	**1, 5, 19-20, 30**
Inventive step (IS):	Yes:	Claims	**4, 6**
	No:	Claims	**1-3, 5, 7-39**
Industrial applicability (IA):	Yes:	Claims	**1-39 (see separate sheet)**
	No:	Claims	

2. Citations and explanations

see Annex

D1: US-A-5,399,346 (ANDERSON W. FRENCH ET AL) March 21, 1995
D2: US 2002/034495 A1 (ANDERSON W. FRENCH ET AL) March 21, 2002
D3: WO 01 75131 A (UNIV TECHNOLOGY CORP) October 11, 2001

*D4: Molecular Biotechnology 5(3), 259-261 (1996) Matthews & Keating
*D5: Bio-Techniques 17(6), 1118-1125 (1994), Clarke et al.

*These documents (not attached) are cited for the first time and are not named in the International Search Report

-- see the citations in the International Search Report

Point 5:

1. Claim 1 is not clear in its formulation, since it relates not only to a method in which whole blood (cells) are transformed without prior separation from (blood) cells.

   Claim 5, which depends on claim 1, makes this clear, namely that claim 1 is also to include methods which are neither novel nor inventive, since they substantially solely comprise the isolation of blood cells and subsequent transformation of the same (see page 2, paragraph 2 and the documents D1 and D2: Transfection of various blood cell fractions/types).

2. Page 6, lines 14-17 in this connection makes the essence of the invention clear, namely that the transformation of blood takes place in the manner such that the blood cells to be transformed are *not* separated beforehand from the other blood components of the removed blood, i.e., are not fractionated.
   A corresponding formulation as given in this passage could remove the lack of clarity in the scope of claim 1.

3. Method for the transformation of cells by means of micro glass beads as one of the possible transformation methods are known, so that claims 19-20 and 30 are not considered to be novel, and claim 16 not as inventive (Yeast: page 2, paragraph before last; Mammalian cells; D4 and D5).

   The blood cell transformation/transformation of different blood cell types is somewhat described in D1 and D2.
   In the transformation of blood cells with micro glass beads, nothing inventive can be recognized, in the light of the above.

   Thus claims 1-3, 5, 7-15 and 17, 20-24 and 30-34 are not inventive.

4. Claim 25 and 35 is not clear: What is the given medicament to consist of?

   Claim 25 and 35 is furthermore not inventive as regards D1 and D2, which describe transformed blood cells for therapy.

   In claims 25-29 and 35-39, accordingly nothing inventive can be recognized.

5. Relating to this, it is to be remarked that the bare establishment of a successful therapeutic application)"therapeutic applications...with the systems described here"; page 35) without more precise data of measurement results or data, is not sufficient for the demonstration of an inventive step.

   The Applicant has shown substantially without doubt that the transformation of whole blood by means of coated glass beads leads to an expression of the DNA used (cDNA for IL-1Ra) in the corresponding IL-1 receptor antagonist protein IL-1Ra, which lies above the control values (Fig. 8/page 28; Fig. 9/page 34).

6. Claims 35-39 contain all the essential features of claims 25-29. This likewise holds for claims 30-34 and 20-24.

   For the sake of clarity and conciseness, these former claims are therefore not to be independent claims, but are only to be formulated as dependent on the latter claims.

7. Claim 18 is unclear and should contain the reference to a method which is described or makes reference to a claim.

8. For giving an opinion on the question as to whether the subjects of the present claim 17 are industrially applicable, there are no single criteria in the convention states. Patentability can also depend on the formulation of the claims. For example, the EPA does not recognize as industrially applicable the subject of claims directed to the medical use of a compound; however, claims can be allowed which are directed to the first medical application of a known compound and the use of such a compound for the production of a medicament for a novel medical application.

ART 34 AMDT

NOT ENTERED CANCELLED OUT ORIGINAL CLAIMS

New Claims

1. Method for producing an induced serum composition from blood, wherein blood cells contained in blood are transiently or stably transformed with at least one nucleic acid molecule, preferably a nucleic acid molecule which codes for at least one therapeutically and/or diagnostically important protein or an effector molecule, and an induced blood composition is obtained whose blood cells transiently or stably express and secrete the therapeutically and/or diagnostically important protein and/or the effector molecule, and wherein the cells are then separated from the serum and an induced serum composition is obtained.

2. Method according to claim 1, wherein the induced blood composition is a blood composition which contains a therapeutically and/or diagnostically important protein in higher concentration than an untransformed blood composition, for example cytokines such as natural or modified IL-1Ra (IRAP, Interleukin-1 receptor antagonist).

3. Method according to claim 1, wherein the induced blood composition is a blood composition in whose blood cells at least one effector molecule, preferably protein or RNA, is expressed, which in untransformed blood cells is expressed not at all, or not in this amount.

4. Method according to one of the foregoing claims, wherein the blood is removed from a patient in a removal system and the blood is transformed with the at least one nucleic acid molecule in the removal system, without the blood cells to be transformed being separated from other blood components.

5. Method according to one of claims 1-4, wherein blood is removed from a patient with a removal system, blood cells, particularly nucleated cells, are separated from other blood components, the blood cells are transformed and are incubated in a medium with or without serum or in pure serum.

6. Method according to one of claims 1-3, wherein the blood is removed from a patient with a removal system, filled into another vessel and transformed in this vessel without the blood cells to be transformed being separated from other blood components.

7. Method according to one of the foregoing claims, wherein the nucleic acid molecule, particularly DNA or RNA, immobilized on solid supports, for example large or small beads, for example of glass, or magnetic small spheres or the wall of the syringe, is used for transformation.

8. Method according to one of the foregoing claims, wherein the nucleic acid molecule, particularly DNA or RNA, possibly labeled with a labeling substance, is used for the transformation.

9. Method according to one of the foregoing claims, wherein the nucleic acid molecule, particularly DNA or RNA, is transformed with an additive which increases the transfection and/or

expression of the nucleic acid molecule.

10. Method according to one of the foregoing claims, wherein the nucleic acid molecule is transformed by electroporation.

11. Method according to one of the forgoing claims, wherein the nucleic acid molecule codes for a molecule which induces, promotes, or regulates the expression of a protein belonging to own body, for example, an anti-sense construct, RNA element, transcription factor, or a transposable element.

12. Method according to one of the forgoing claims, wherein the nucleic acid molecule is contained in a vector, for example, in a plasmid or in a virus.

13. Method according to one of the forgoing claims, wherein the nucleic acid molecule is present functionally connected to at least one regulatory element, for example, a promoter, enhancer, or intron, particularly a blood cell specific regulatory element.

14. Method according to one of the forgoing claims, wherein the nucleic acid molecule is present, functionally connected to nucleotide section coding for a signal peptide for protein secretion from the cell.

15. Method according to one of the forgoing claims, wherein the at least one nucleic acid molecule is transformed using liposomes, viral vectors or bound to micro glass beads.

16. Method for the transformation of cells, particularly of cells contained in blood, for example blood cells, with nucleic acid molecules, wherein the cells or blood cells are brought into contact with the nucleic acid molecules, the cells or the blood cells present in the blood are transformed and stably or transiently transformed cells or blood cells are obtained, and wherein the nucleic acid molecules are covalently bound, in particular with acid lability, to micro glass beads.

17. Method for treating the human or animal body, wherein blood is removed, preferably with a syringe, from the human or animal body, a method according to claims 1-15 is performed and the induced serum composition is reapplied to the human or animal body after separation of the transformed blood cells and blood components.

18. Use of micro glass beads, particularly micro glass beads having bound nucleic acids, for the transformation of whole blood, in particular nucleated cells in whole blood, in particular for the expression and secretion of proteins in blood, particularly blood cells.

19. Use of micro glass beads, particularly micro glass beads having bound nucleic acids, for the transformation of biological cells, particularly animal, plant, or human cells.

20. Use of blood, particularly whole blood, for the transformation of blood cells with nucleic acid molecules coding for therapeutically and/or diagnostically important proteins or effector

molecules.

21. Use of blood, particularly whole blood, for the transformation of blood cells with nucleic acid molecules, coding for therapeutically and/or diagnostically important proteins or effector molecules, for the treatment of leukemia.

22. Use of blood, particularly whole blood, for the transformation of blood cells with nucleic acid molecules coding for therapeutically and/or diagnostically important proteins or effector molecules, for the treatment of traumatic, degenerative, chronic inflammatory diseases of the nervous system.

23. Use of blood, particularly whole blood, for the transformation of blood cells with nucleic acid molecules coding for therapeutically and/or diagnostically important proteins or effector molecules, for the treatment of traumatic, degenerative, chronic inflammatory diseases of the motor apparatus.

24. Use of blood, particularly whole blood, for the transformation of blood cells with nucleic acid molecules coding for therapeutically and/or diagnostically important proteins or effector molecules, for the treatment of traumatic, degenerative, chronic inflammatory diseases of the internal organs.

25. Use of blood for the production of a medicament for the transformation of blood cells of the blood with nucleic acid molecules coding for therapeutically and/or diagnostically important proteins or effector molecules.

26. Use of blood for the production of a medicament kit for the treatment of leukemia.

27. Use of blood for the production of a medicament for the treatment of traumatic, degenerative, chronic inflammatory diseases of the nervous system.

28. Use of blood for the production of a medicament for the treatment of traumatic, degenerative, chronic inflammatory diseases of the nervous system.

29. Use of blood for the production of a medicament for the treatment of traumatic, degenerative, chronic inflammatory diseases of the nervous system.

30. Use of nucleic acid molecules, particularly coding for therapeutically and/or diagnostically important protein or effector molecules for the transformation of blood or blood cells according to the method of claim 16 and the expression and secretion of therapeutically and/or diagnostically important proteins or effector molecules.

31. Use of nucleic acid molecules, particularly coding for therapeutically and/or diagnostically important protein or effector molecules for the transformation of blood or blood cells and the expression and secretion of therapeutically and/or diagnostically important proteins or effector molecules for the treatment of leukemia

32. Use of nucleic acid molecules, particularly coding for therapeutically and/or diagnostically important protein or effector molecules for the transformation of blood or blood cells and the expression and secretion of therapeutically and/or diagnostically important proteins or effector molecules for the treatment of traumatic, degenerative, chronic inflammatory diseases of the nervous system.

33. Use of nucleic acid molecules, particularly coding for therapeutically and/or diagnostically important protein or effector molecules for the transformation of blood or blood cells and the expression and secretion of therapeutically and/or diagnostically important proteins or effector molecules for the treatment of traumatic, degenerative, chronic inflammatory diseases of the motor apparatus.

34. Use of nucleic acid molecules, particularly coding for therapeutically and/or diagnostically important protein or effector molecules for the transformation of blood or blood cells and the expression and secretion of therapeutically and/or diagnostically important proteins or effector molecules for the treatment of traumatic, degenerative, chronic inflammatory diseases of the internal organs.

35. Use of nucleic acid molecules, particularly coding for therapeutically and/or diagnostically important protein or effector molecules for the production of a medicament for the transformation of blood or blood cells according to the method of claim 16.

36. Use of nucleic acid molecules, particularly coding for therapeutically and/or diagnostically important proteins or effector molecules, for the production of medicaments for the treatment of

leukemia.

37. Use of nucleic acid molecules, particularly coding for therapeutically and/or diagnostically important proteins or effector molecules, for the production of medicaments for the treatment of traumatic, degenerative, chronic inflammatory diseases of the nervous system.

38. Use of nucleic acid molecules, particularly coding for therapeutically and/or diagnostically important proteins or effector molecules, for the production of a medicament for the treatment of traumatic, degenerative, chronic inflammatory diseases of the motor apparatus.

39. Use of nucleic acid molecules, particularly coding for therapeutically and/or diagnostically important proteins or effector molecules, for the production of medicaments for the treatment of traumatic, degenerative, chronic inflammatory diseases of the internal organs.